REMARKS

Claims 1 and 4-9 are pending in this application. Claims 2 and 3 have been cancelled without prejudice or disclaimer. Applicants reserve the right to file one or more divisional, continuation, or continuation-in-part applications directed to any withdrawn or canceled subject matter.

Claims 1, 7, 8 and 9 have been amended to more particularly point out and distinctly claim the invention.

New claims 10-14 have been added. Support for the new claims may be found throughout the application for example in paragraphs [0024] and [0029].

No new matter has been added by the amendments.

Applicants wish to thank the Examiner for taking the time to meet with their representatives for an interview on October 2, 2009.

1. The Rejections Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 1 and 4-9 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentably obvious over the combination of Tabuchi *et al., Ann Otol Rhinol Laryngol*. 2002 Jan; 111(1):44-9 ("Tabuchi") in view of U.S. Patent No. 6,265,370 ("Donovan").

The currently pending claims are directed to a method for treating tinnitus induced by cochlear excitotoxicity in a human, the method comprising administering to the human a therapeutically effective amount of a pharmaceutical composition comprising the NMDA receptor antagonist ketamine, effective to suppress or reduce NMDA receptor mediated aberrant activity of the auditory nerve in a the human in need of such treatment and correlating the administration of ketamine with a reduction in tinnitus.

According to the Examiner, Tabuchi teaches that ketamine has a protective effect against cochlear dysfunction induced by transient ischemia. Moreover, the Examiner argues that ischemia induces acute swelling of afferent dendrites of the basal side of the inner hair cells which "strongly" indicates excitoxicity is induced in the ischemic cochlea. Office Action of April 1, 2009, page 3, lines 3-7

The Examiner concedes, however, that Tabuchi does not teach the treatment of tinnitus or local drug administration. Office Action of August 5, 2009, page 5, lines 8-10.

The Examiner argues that Tabuchi's shortcomings are nevertheless supplemented by Donovan's disclosure that tinnitus is due to cochlear nerve dysfunction resulting from disturbances of the synapses between cochlear hair cells and afferent dendrites of the auditory nerves. Office Action of April 1, 2009, page 3, line 21 to page 4, line 2.

The Examiner concludes, therefore, that the combination of Tabuchi and Donovan would have rendered the use of ketamine for the treatment of tinnitus in the manner claimed, obvious to the person of skill in the art. Office Action of April 1, 2009, page 4, lines 2-10. Applicants respectfully disagree with the Examiners characterizations and conclusions, and traverse as follows.

Applicants respectfully assert in the alternative that:

- A person of skill in the art would not have been motivated to combine Donovan and Tabuchi in developing the claimed methods of treating tinnitus because the references 'teach away' from one another;

- Even if they would have been motivated to combined Donovan and Tabuchi, the person of skill in the art would not have had a reasonable expectation that the combination would yield a successful treatment of tinnitus as claimed; and

- Even if they would have had a reasonable expectation of success of treating tinnitus with ketamine in the manner claimed in the subject application; the invention nevertheless provides results that meet a long felt and unmet need and which overcome the failure of others to provide suitable treatments for tinnitus.

Applicants are submitting herewith a declaration under 37 CFR § 1.132 by Dr. Richard Salvi ("Salvi Declaration") in support of these arguments.

In *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992), the Federal Circuit held that the USPTO should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention. See also *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

1.1 There is no motivation to combine Tabuchi and Donovan to develop the claimed methods for treating tinnitus

1.1.1 Tabuchi itself teaches away from using ketamine to treat tinnitus as claimed

A scientist reading Tabuchi in March 2004, would have been dissuaded from using NMDA receptor antagonists such as ketamine, in the treatment of any disorder associated with excitotoxicity involving the inner hair cell auditory nerve synapses. Salvi Declaration ¶ 19.

Referring to Tabuchi, the Examiner states that ischemia induces acute swelling of afferent dendrites of the basal side of the inner hair cells which "strongly" indicates excitoxicity is induced in the ischemic cochlea. Office Action of April 1, 2009, page 3, lines 3-7.

However, Tabuchi is silent as to what effect, if any, ketamine might have on ischemia-induced swelling of the radial dendrites. Salvi Declaration ¶ 21.

Rather, Tabuchi specifically states that NMDA receptor antagonists "do not have any protective effect on cochlear ischemia-reperfusion injury" and in fact, *delay* recovery from excitoxicity. Tabuchi page 48, left column; Salvi Declaration at ¶¶ 20 and 22. Whatever non-NMDA pathway was exploited by ketamine to partially reduce compound action potential ("CAP") threshold shifts following transient ischemia in Tabuchi, it must be kept in mind that ketamine nevertheless retains its NMDA-receptor antagonism as its primary pharmacological characteristic. Salvi Declaration ¶ 22.

Paragraph [0063] of the subject application describes an experiment wherein the NMDA receptor antagonists ketamine and 7-chlorokynurenate ("7-CK") were demonstrated to in fact, *delay* hearing recovery following acute acoustic trauma compared to untreated animals in a manner consistent with what would have been predicted by Tabuchi. See also Figures 4A and 5A of the subject application. Salvi Declaration ¶ 23.

Therefore, even though ketamine might be able to partially reduce CAP threshold shifts through some non-NMDA pathway, ketamine nevertheless remains an NMDA-receptor antagonist which according to Tabuchi is likely to delay recovery from excitoxicity in inner hair cell auditory nerve synapses. Salvi Declaration ¶ 22.

Applicants respectfully assert that the Examiner has not addressed why Tabuchi's teaching that NMDA receptor antagonists "do not have any protective effect on cochlear

ischemia-reperfusion injury" and in fact, *delay* recovery from excitoxicity; would motivate one of skill in the art to use an NMDA-receptor antagonist such as ketamine to treat tinnitus associated with excitotoxicity. Beyond speculation relating to nitric oxide antagonism and dopamine release up-regulation, Applicants remind the Examiner that Tabuchi fails to provide a specific mechanism by which ketamine improves CAP threshold shifts. Salvi Declaration ¶ 21.

1.1.2 Tabuchi teaches away from a combination with Donovan

Donovan states that a particular form of inner ear tinnitus results from functional disturbances of the synapse between cochlear hair cells and afferent dendrites of the auditory nerve. Donovan implies that there is an excessive release of glutamate at the afferent cochlear synapse. (Donovan at 2:54-62). Salvi Declaration at ¶ 25. Donovan, therefore, implies that too much glutamate at the afferent cochlear synapse results in overstimulation of its glutamate receptors and leads to excitoxicity. Salvi Declaration at ¶ 26.

Even if Tabuchi suggested the use of ketamine in tinnitus in the manner claimed (Dr. Salvi agrees in ¶27 of his declaration that it does not), Donovan would have dissuaded a person of skill in the art at the time of filing of the subject application, from trying such a treatment because it also implies that the tinnitus is a result of excitoxicity. Salvi Declaration at ¶ 27.

Specifically, skilled artisan would have found that Tabuchi taught away from Donovan, because they would not have wanted to treat the ostensible excitoxicity-associated tinnitus described in Donovan by *delaying* recovery from the excitoxicity with an NMDA receptor antagonist such as ketamine as described in Tabuchi. Salvi Declaration ¶ 27.

It is improper to combine references in the context of a § 103 rejection, where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983); MPEP 2145.

1.1.3 Donovan teaches away from a combination with Tabuchi

According to Tabuchi, ketamine can improve CAP threshold shifts following transient ischemia compared to control through some non-NMDA pathway. Salvi Declaration at ¶¶ 20

and 22. Tabuchi speculates that this non-NMDA pathway might be associated with *dopamine release up-regulation*. Tabuchi page 48/49 bridging paragraph; Salvi Declaration at ¶28.

Donovan advocates the use of botulinum toxin ("Botox") in the treatment of tinnitus. However, Donovan states that Botox inhibits the release of dopamine and glutamate. (Donovan at 4:41-49) As such, one of skill in the art reading Donovan, would have been led to believe that tinnitus treatment should be associated with a *reduction in dopamine release*.

Therefore, a person of skill in the art would not have used an agent such as ketamine – which according Tabuchi might be associated with dopamine release up-regulation – for the treatment of tinnitus as claimed. Accordingly, a person of skill in the art at the time of filing of the subject application reading Donovan's assertion that that tinnitus treatment should be associated with a *reduction in dopamine release*; would have felt that Donovan taught away from Tabuchi which speculates that ketamine is associated with *dopamine release up-regulation*. Salvi Declaration ¶ 28; *Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779.

1.1.4 The modification of Donovan by Tabuchi would have changed the principles of tinnitus treatment suggested in Donovan

Given that Tabuchi teaches that use ketamine is: 1) associated with a *delay* in recovery from excitoxicity; and 2) speculated to be associated with dopamine release up-regulation and not reduction; the skilled artisan would have felt that the use of ketamine in tinnitus treatment as claimed would change the principles of tinnitus treatment suggested in Donovan. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01. Therefore, for either one of these reasons of this paragraph, the teachings of the references are insufficient to render the claims *prima facie* obvious.

1.2. Donovan and Tabuchi would not have provided a reasonable expectation for a successful treatment of tinnitus as claimed

The Federal Circuit has held that "[o]bviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re Kubin,* 2008-1184, (Fed. Cir. 2009) citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). As such, even

though an invention may be "obvious to try," it nevertheless remains patentable if the cited prior art combination fails to provide one of skill in the art (at the time of filing of the relevant application) with "a reasonable expectation of success."

Even if they would have been motivated to combine Donovan and Tabuchi, given the wide range of pathologies and lesions associated with cochlear dysfunction and the wide range of symptoms that could result from it; as well as the large numbers of failed drug treatments, a person skilled in the art would not have reasonably expected that treatment of one symptom associated with cochlear dysfunction, e.g., hearing loss, would be effective in the treatment of another, e.g., tinnitus. Salvi Declaration ¶¶13, 29-37.

Dr. Salvi stated that many compounds were tested prior to March 2004 for their ability to reduce hearing loss. Salvi Declaration ¶14. However, he knew of none that were effective in the treatment of both hearing loss and tinnitus. Salvi Declaration ¶14. He described how the drug caroverine was tested for both indications but was ultimately abandoned because it was "unable to ameliorate tinnitus in a significant manner." Salvi Declaration ¶14.

Dr. Salvi also described how D-JNKI-1 was known to prevent acoustic trauma-induced permanent hearing loss in a dose-dependent manner by providing protection against neuronal death and loss of cochlear hair cells. Salvi Declaration ¶15. Using the logic of the current §103 rejection – where the a potential treatment of hearing loss associated with cochlear dysfunction would provide a reasonable expectation that the same treatment would be useful for tinnitus associated with cochlear dysfunction – the skilled artisan should have had a reasonable expectation that the D-JNKI-1 would also be useful in the treatment of tinnitus associated with cochlear dysfunction.

However, the experiment described in Paragraphs [0062-0064] of the subject application shows the opposite. It shows how D-JNKI-1 – similar to untreated control animals – failed to decrease the number of behavioral correlates of tinnitus in an animal model. Salvi Declaration ¶15. As such, the experiment actually demonstrates how yet a further potential treatment of hearing loss associated with cochlear dysfunction, is ineffective at treating tinnitus associated with cochlear dysfunction

Tabuchi adds no additional guidance in this regard. Tabuchi merely discloses how ketamine and dextromethorophan were able to moderately improve CAP threshold shifts. The CAP is a physiological measure arising from the synchronous discharge of auditory nerve fibers

in response to the onset of a suprathreshold *sound* stimulus. In contrast, tinnitus is a subjective auditory sensation that occurs in the *absence* of external sound stimulation. Salvi Declaration ¶16

This is why Dr. Salvi stated that the CAP, "cannot be used to make *any logical inference*" about the presence or absence of tinnitus which is a subjective phenomenon that requires a behavioral response from a patient indicating he/she is experiencing a phantom auditory sensation. [emphasis added] Salvi Declaration ¶17. Accordingly, Dr. Salvi concluded:

> The protective effects of ketamine on CAP measurements would, therefore, not have taught a scientist in March 2004 *anything* about the efficacy of using ketamine to treat tinnitus as claimed. As such, the protective effects of ketamine on the CAP measurements *would not have provided a scientist of the time with a reasonable expectation* that ketamine would be effective in treating tinnitus as claimed [emphasis added]

Salvi Declaration ¶17. The Examiner finds support for the required "reasonable expectation of success" in the fact that Tabuchi conducted their CAP shifting experiments *in vivo*. Office Action of April 1, 2009, page 5, lines 4-5. However, given that CAP threshold experiments would not have taught the skilled artisan, "*anything* about the efficacy of using ketamine to treat tinnitus," the fact that Tabuchi's experiments were performed *in vivo* is irrelevant. Salvi Declaration ¶17.

Therefore, in view of the failure of caroverine and D-JNKI-1 (and many other drugs see Salvi Declaration ¶¶29-37) to treat tinnitus, the person of skill in the art in March 2004 would not have had a reasonable expectation that a therapy potentially effective for the treatment of hearing loss associated with cochlear dysfunction would also be successful in treating tinnitus as claimed. Salvi Declaration ¶18; *O'Farrell*, 853 F.2d 894, 903

Dr. Salvi specifically states, "the fact that Tabuchi's experiments were done *in vivo* would not have impacted this conclusion." Salvi Declaration ¶17.

1.3 There is sufficient secondary evidence of non-obviousness to rebut any *prima facie* case of obviousness

The Supreme Court has held that there can be additional factors (i.e., "secondary considerations" of non-obviousness) that militate against an invention being considered unpatentably obvious. *Graham v. John Deere Co.,* 383 U.S. 1 (1966).

Applicants respectfully assert that even if the skilled artisan would have combined Tabuchi and Donovan; and even if they would have had a reasonable expectation of success of treating tinnitus with ketamine in the manner claimed in the subject application (Applicants emphatically reject both points); the invention *nevertheless* provides results that meet a long felt and unmet need and which overcome the failure of others to provide suitable treatments for tinnitus. These results are sufficient to rebut any colorable prima facie case of obviousness.

Tinnitus is very common in the population and its history goes all the way back to the Egyptians. Many patients suffer severely from tinnitus as it can affect everyday activities considerably. Salvi Declaration ¶29.

Applicants respectfully submit that prior to March 2004, many investigators tried and failed to develop suitable pharmacological therapies for the treatment of tinnitus. In fact, none of the treatment options available in March of 2004 was able to achieve a lasting effect and therapeutic success. Salvi Declaration ¶¶ 30-37.

As such, there has been a well documented and long felt need for methods of treating tinnitus. Moreover, researchers and investigators have consistently failed over the years to meet this need.

In August 2008, the assignee of the subject application – Auris Medical AG – reported the results of the first phase I/II clinical trial with "AM-101," its investigational ketamine-based drug for the treatment of inner ear tinnitus. The double blind, randomized clinical trial with placebo control involved four study sites in Germany and had the evaluation of AM-101's safety as primary objective. As a secondary objective, the potential efficacy of AM-101 was evaluated. The study results show that intratympanically injected AM-101 was well tolerated by study participants. The clinical trial provided first indications for the potential efficacy of AM-101 in the treatment of inner ear tinnitus. The clinical data suggest that AM-101 has a positive effect on the perceived loudness of tinnitus as well as on its maskability; in addition, a positive trend was observed overall.

In March 2009, Auris Medical AG announced that it began a phase IIb clinical trial of AM-101. The study is designed as a double blind, randomised, placebo-controlled trial with parallel dose groups and will take place in Germany, Belgium and the Netherlands.

As such, Dr. Salvi concludes that,

> In view of the long felt need for effective treatments of tinnitus and the failure of others to identify suitable therapies; the invention of the use of ketamine for the treatment of tinnitus as claimed and described in the '298 application represents a *significant breakthrough*. [emphasis added]

Salvi Declaration ¶ 39.

1.4 Summary

Applicants respectfully request withdrawal of the current rejection under § 103 because:

- A person of skill in the art would not have been motivated to combine Donovan and Tabuchi in developing the claimed methods of treating tinnitus because the references 'teach away' from one another;

- Even if one would have been motivated to combine Donovan and Tabuchi, the person of skill in the art would not have had a reasonable expectation that the combination would yield a successful treatment of tinnitus as claimed; and

- Even if they would have had a reasonable expectation of success of treating tinnitus with ketamine in the manner claimed in the subject application; the invention nevertheless provides results that meet a long felt and unmet need and which overcome the failure of others to provide suitable treatments for tinnitus.

2. Conclusion

Applicants believe the claims are allowable and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful to resolving any issues.

It is believed no fees are due; however, the commissioner is authorized to charge any fees and credit any overpayments to Deposit Account No. 50-5071 which may be due.

Respectfully submitted,

Date: January 7, 2010

/Thomas Haag/
By: Thomas A. Haag, Ph.D., Esq.
Reg. No. 47,621

Fanelli Strain & Haag PLLC
Customer No. 0091436
1455 Pennsylvania Avenue, N.W.
Suite 400
Washington, D.C. 20004
Telephone: 202.621.1840